Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

September 13, 1999

Rec'd 9/14/99

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Response to Supplements and Other Changes to an Approved Application; Proposed Rule; (Federal Register, 28-June-99, Docket No. 99N-0193)

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the above referenced proposed rule. Specific comments, identified by citation, are provided in tabular form in the enclosure.

It is Novartis' position that the draft revision to CFR 314.70 and CFR 601.12 and associated draft Guidance (Docket 99D-0529) would be improved with additional clarification of certain elements contained therein. Simplification of the regulatory filing requirements and submission types (Prior Approval, Changes Being Effected, Annual Report) is also warranted, as the proposed rule relies on change assessment data submitted with the proposed change to justify the change. The rule as proposed does not significantly address reduction of filing requirements in light of the additional information provided at filing as compared with current practice.

As previously noted in Novartis' comments to Docket No. 99D-0529, the numerous cross references to other guidance documents, some of which have not been seen yet in draft form, contribute to potentially contradictory regulatory interpretations, and do not provide the benefits of regulatory relief envisioned under FDAMA.

Further, several presentations and discussions occurred at the FDA Public Meeting of August 19, 1999 concerning this draft rule and proposed draft Guidance. Novartis concurs with the PhRMA recommendations that appropriate evaluation and issuance of these key regulatory documents require the Agency to closely consider the issues of conflicting, confusing, or otherwise contradictory regulatory guidances, and also to consider the wisdom of implementing the draft Guidance (Docket No. 99D-0529) prior to finalization of the proposed rule 314.70. Novartis therefore recommends that the Agency:

- publish a formal second draft with an additional review and comment period, for a revised version of this proposed Rule which incorporates comments from all involved parties received during the first review period, and;
- take advantage of industry and public involvement in development of a rule and associated guidance, which more strongly implement the spirit of FDAMA.

99D-0529

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Thank you for the opportunity to comment. If you have any questions, please contact Dr. Mathias Hukkelhoven at (973)-781-6035 or Joan A. Materna at (973) 781-3379.

Sincerely,

M. Hukkelhoven

Dr. Mathias Hukkelhoven
Vice President, Head US DRA
Drug Regulatory Affairs

Enclosures: Comments provided in duplicate
Response to Draft Proposed Rule 314.70/601.12

Novartis' Comments on the Proposed Rule 314.70 and 601.12

Section	Comments
314.70(a)(6)	Listing of all changes in the cover letter of the Supplement or Annual Report carries inadvertent risk of loss of confidentiality should the documents be requested under FOI. We suggest an appendix or summary exempt from FOI requests, which may be attached to the Supplement/Annual Report as a way to provide the requested information to the FDA.
314.70(b)(1)	The statement that "**any** change in the production process or equipment that has a **substantial potential** to have an adverse effect on identity, strength, quality, purity or potency as these factors may relate to the **safety or effectiveness** of the product" needs to be clarified, so the moderate to minor changes which are within the requirements are not submitted for Prior Approval.
314.70(b)(2)(i)	Please add the statement that changes to meet a new compendia are a permitted exception to this section.
314.70(b)(2)(v)	Clarify "labeling" to indicate "drug product labeling" so that drug substances and product intermediates are not included in this statement
314.70(b)(2)(vii)	Delete the reference to natural products, or clarify the definition. It is not clear whether fermentation product-based drug substances are considered natural products, or why a separate set of requirements would be relevant.
314.70(b)(3)(viii)	Delete references to SOPs. It is not clear why the Agency would require a list of relevant SOPs for changes when they are not submitted in any application; SOPs are generally considered under cGMP.
314.70(c)(2)(ii)(B) and 314.70(d)(2)(iii)	Clarify the difference between equipment that is "similar but not identical", which is proposed to be a CBE-30, and the SUPAC terminology of equipment of the "same design and operating principle", which is already defined in the SUPAC guidance and the proposed rule as an Annual Reportable change. The difference is not readily apparent and may lead to varying interpretations of regulatory submission requirements.
314.70(c)(4) and (5)(ii)	A timeline and dispute resolution process needs to be defined by regulation or guidance, in particular as there is latitude to interpret what may be required to validate the effect of the change, and for FDA to determine that "*compliance with this section is achieved*". This is in line with the stated aim of greater consistency in FDA approach and reduced regulatory burden consistent with the public health. Excessive recommendations for BA studies or extensive analytics should be avoided.
314.70(c)(5)(ii)	If necessary information is not included in a typical SNDA CBE, is the FDA determination of compliance with the requirements of this section (with the addition of more information) equivalent to an approval of the supplement?
314.70(c)(6)	Please separate this type of submission out from the CBE requiring 30 days notice. For example, leave CBE-30 days as 314.70(c), change CBE-0 to 314.70(d), change annual reports to 314.70(e), etc. This shows there are 4 potential filing categories (instead of 3, one with 2 subclasses). This will simplify the rule and regulatory filing strategy.
314.70(c)(7)	If the Agency disapproves of the CBE supplement, then the sponsor should be notified within 30 days of this submission as per 314.70(c)(5)(ii).
314.70(d)(2)(i)	Change to read "any change made to comply with an official compendium".

	The sponsor is directed by FDA Guidance that the USP is the responsible compendial body for regulatory specifications. This is further supported by Section 501(b) of the FD&C Act. Therefore, the sponsor should be able to rely on the USP, and the available compendial review process, rather than to be placed between USP and FDA during regulatory review.
314.70(d)(2)(ii) and 601.12(d)(2)(ii)	Change text to read "*deletion, reduction or replacement with a color previously used in other CDER/CBER approved products*"
314.70(d)(2)(vi)	Production lots should be defined in the Definitions section to include validation/scale-up batches manufactured by the representative production process within a ten-fold batch size for consistency with SUPAC/BACPAC.
314.70(d)(2)(iii)	The replacement of equipment of the same design and operating principles should not need to be reported. For consistency with the existing SUPAC guidances, a SUPAC subclass change is required to precipitate a filing.
314.70(d)(2)(iv)	Delete "containing the same number of dosage units". For nonsterile solid dosage forms, the fill count of the bottle may be permitted to change as the bottle size/shape changes. This would prevent a situation of excessive headspace in a new container size.
314.70(d)(3)(i)	The term "validated" should be changed to "evaluated, as appropriate" or "assessed, as appropriate" to avoid confusion with the established cGMP concept of validation.
314.70(d)(3)(iii)	Annual Reports are requested to contain a cross reference to validation protocols and SOPs. Although "validate" is defined in the section to exclude process and equipment validation, the use of similar words in unrelated contexts will engender confusion within industry and the FDA. It is burdensome to have multiple types of validation protocols, some of which require FDA submission and some of which are retained at the facility for cGMP inspection by FDA field personnel. SOPs are generally considered cGMP documents.
314.70(d)(3)	If the same changes are proposed for multiple products, would the FDA want to be notified as to all of the products that are affected in all annual reports? This would not seem to make sense from a timing perspective, as annual reports are not submitted simultaneously. Please clarify the statement.

HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CROSS REFERENCE SHEET

Docket Number/Item Code: 99N-0193/C26

See Docket Number/Item Code: 99D-0529/C35

NOVARTIS PHARMACEUTICAL CORPOR
(973)781-8769
INTERNAL DISTRIBUTION
101 - MAILROOM - 091399
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